CLINICAL PRACTICE

Acute Convulsive Seizures: When is It Too Early to Treat?

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ABSTRACT

Acute convulsive seizures are overwhelming events that require immediate attention from clinicians and practitioners, especially when witnessed in a hospital setting. Adequate management of inpatient-witnessed seizures lies in understanding the time-related pathophysiologic stages of the seizure. The anatomical location of the seizure origin is as important as seizure stage but might not be easy to determine in the acute setting, especially if the seizure is nonfocal. Although investigating and treating the cause of a seizure has high priority, understanding the interplay between the pathophysiologic responses and the various bodily responses are crucial in treatment. This interplay has interesting dynamics that change within minutes. Knowing such dynamics allows clinicians and practitioners to choose their best treatment options in the best time interval when a seizure occurs in an acute care facility. Our commentary provides an overview of such dynamics and how they can change the misconceptions that many clinicians and practitioners have in dealing with an acute convulsive seizure.

INTRODUCTION

Acute convulsive seizures occur at least once in about 10% of the population younger than age 85 years.[1] These seizures are frequently seen in most health care facilities. They can occur in a hospital's Emergency Department, postoperative recovery room, Intensive Care Unit, inpatient wards, and rehabilitation ward, as well as outpatient clinics and nursing homes. Most community hospitals do not have dedicated inpatient wards for patients with seizures, and some do not even have a dedicated neurology ward. Even some university medical centers and their affiliated hospitals do not have a dedicated neurology ward. Thus, the first responders to seizures are frequently neither a neurologist nor a neurologist in training. The main target of this article is to educate these clinicians and practitioners.

TYPES OF SEIZURE

A clinical convulsive seizure is defined as rhythmic convulsions that last less than 5 minutes. It can be partial (affecting one limb or one side of the body and/or the face) or generalized (affecting the whole body). In partial seizures, consciousness is usually preserved unless they are partial complex seizures. In generalized seizures, consciousness is always impaired unless they are psychogenic nonepileptic seizures.[1] Although a single limb convulsion is the most common presentation of a partial seizure, generalized seizures can appear in several forms from the start or can become generalized from a focal seizure.

Tonic-clonic seizures are the most common presentation of generalized seizures in adults. They start with a tonic phase in which the limbs appear to spastically contract toward the body, followed by their extension and rhythmic jerking. Tonic generalized seizures consist of constant muscle contraction. Clonic generalized seizures consist of constant rhythmic jerking from the start. Myoclonic seizures are usually composed of a group of muscles or the entire body jerking, jumping, or flinging out in a sudden unpredictable way. Atonic seizures usually present as episodes of a sudden fall or collapse caused by sudden loss of muscle tone. This type of seizure is usually confused with cardiac arrhythmias and other pathologies. It is usually suspected after a cardiac cause is ruled out.

Finally, absence seizures are a type of generalized seizure that usually starts in childhood but can continue in adulthood. This seizure type is composed of a sudden stare with unresponsiveness. It can be accompanied with blinking or a slight head turn. It might be confused with a partial complex seizure except that the latter is usually preceded by an aura and accompanied by automatisms.[2] Once the seizure duration passes 5 minutes, or convulsions recur within a 5-minute period without return of consciousness, it is called convulsive status epilepticus (whether partial or generalized) according to the currently operational newer guidelines.[3,4]

TREATMENT

Early administration of benzodiazepines has been well established as the first treatment option for termination of status epilepticus before internalization of the γ-aminobutyric acid (GABA) A receptors (where benzodiazepines act) in the brain.[5,6] Among some clinicians, there is a misconception that the algorithm of treatment of seizures starts by administering benzodiazepines and escalates to antiepileptic medications such as phenytoin, valproate, phenobarbital, and levetiracetam, ending with sedation and anesthesia. Although this statement is correct for the treatment of status epilepticus, it is incorrect for the treatment of acute convulsive seizures. Treatment of acute convulsive seizures (less than 5-minute duration) starts with supportive care, protecting the airway, and assisting breathing during the seizure. Benzodiazepines should not be given that early except in certain specific conditions. One such situation is when there are numerous and frequent short epileptic seizures with consciousness regained in-between (does not meet criteria of status epilepticus) and especially when there is a known severe underlying epileptic syndrome.[2] This faulty practice might occur for many reasons. One is that the patient might be hypertensive or hypotensive, tachycardic or bradycardic, tachypneic or brachypneic, and in some occasions hypoxic. Although these symptoms are concerning and should be monitored carefully because of the possibility of severe complications such as sudden unexpected death

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in epilepsy,[7,8] the symptoms should not be overwhelmingly managed. Another reason for inappropriate treatment is the dramatic appearance of the patient, which creates a panic situation around him/her. Last but not least is that everyone is expecting the clinician or practitioner to do a heroic measure that matches the dramatic situation when actually the less we do, the better the outcome will likely be. To understand this clearly, we must look at the different stages of a seizure on the physiologic, cellular, and synaptic levels. It is also important to know when the different subtypes of GABA receptor are regulated during a seizure and correlate it with the time when dysfunction of the blood-brain barrier (BBB) occurs.[9]

LOCATION OF THE EPILEPTIC FOCUS AND THE AUTONOMIC RESPONSE

The location of the epileptic focus in the brain might determine the autonomic response from a seizure. The more common is a sympathetic overstimulation. Less commonly, a parasympathetic overstimulation or a mixed overstimulation occurs. Studies have shown that sympathetic overstimulation usually occurs if the right insular cortex is involved, especially the rostral part of it. Similar response occurs if the thalamus or the ventromedial hypothalamus, or both, are involved. If parasympathetic overstimulation is observed, several locations have been identified. These are the left insular cortex, especially the caudal part of it; the cingulate gyrus; the prefrontal cortex; the lateral hypothalamus; or the preoptic hypothalamic area. Involvement of the amygdala usually produces variable responses. Meanwhile, if several foci are involved, they create a nonselective activation, which ends up with either an oscillatory pattern or a dominating pattern. Finally, several cardiovascular and cardiorespiratory reflexes might also interact in determining the dominating pattern.[10]

STAGES OF A SEIZURE

Very Early Stage/Nonstatus Seizures —Less than 5 Minutes

At the very early stages of a seizure (first 5 minutes), peripherally, there is more commonly an increased sympathetic activity within the body. Nonetheless, a dominating response from the parasympathetic system is less common but possible. At the cellular level, the brain increases the production of GABA neuroinhibitor, which is usually sufficient to inhibit the seizure (self-limiting). At the synaptic level, the GABA A-δ_2 subunit receptor (binding site for benzodiazepines) start to upregulate while the GABA A-$\beta_{2/3}$ subunits (binding site for GABA and GABA agonists) also start to upregulate but at a slower rate (Figure 1).

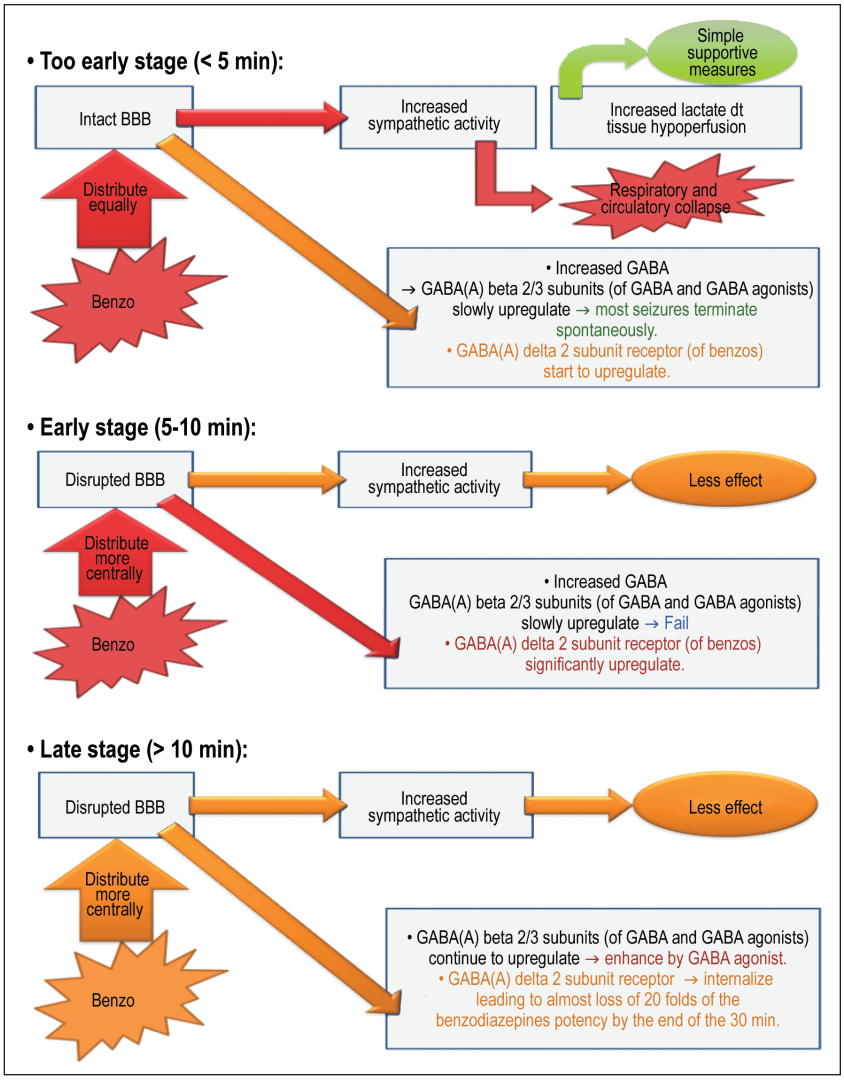

Figure 1. Effect of benzodiazepines on different pathophysiologic pathways of seizure as time progresses.[a]
[a] Red pathway = more potent drug effect; orange pathway = lack of or less potent effect; and light green pathway = supportive measures only are indicated.
BBB = blood-brain barrier; benzo = benzodiazepine; dt = due to; GABA = γ-aminobutyric acid.

Despite this upregulation, the risk of administering benzodiazepines at this very early stage might outweigh the benefit. This is because the BBB is still intact, and thus benzodiazepines are equally distributed peripherally and centrally.[11] On the other hand, at this stage there might be 2 main reasons for hypoxemia. The first is directly from the seizure itself, likely from collapse of the airway during or after the seizure without an adequate support given. There is also an increasing peripheral acidosis secondary to lactate production, which leads to tissue hypoperfusion and hypoxemia. The second reason is potential oversedation produced by benzodiazepines. Although some can blame the respiratory collapse on the seizure itself, the addition of benzodiazepines certainly does

not help the respiratory status, and intubation is imminent if the patient was already compromised from the seizure. Although a benzodiazepine might act centrally to stop the seizure, this medication acts in equal effect peripherally because of the intact BBB. This can lead to suppression of the increased sympathetic activity that is usually required to maintain the bodily demands during a seizure and thus leads to respiratory and circulatory compromise. Less commonly but equally harmful, it might add to the cardiocirculatory depression when a parasympathetic response is dominating. Both mechanisms frequently end up with intubation of the patient and the need for vasopressors.

In summary, benzodiazepines given for a seizure before 5 minutes have elapsed might be effective to abort a seizure but are more harmful because they suppress the associated autonomic response and aggravate the cardiorespiratory compromise produced by a seizure (Table 1). This leads us to a potentially counteracting statement: Too early administration of benzodiazepines is accompanied with more complications than benefits.

Early Stage/Early Status Epilepticus —5 to 10 Minutes

After 5 minutes, many conditions change because the BBB starts to be compromised, allowing more benzodiazepine effect centrally than peripherally. Of course, this is also augmented by the higher level of GABA A-δ_2 subunit receptors (Figure 1).[11-13] Benzodiazepines given for a seizure after 5 minutes have elapsed might be effective to abort a seizure and prevent the potentially profound adverse effects of a prolonged seizure (Table 1).

Intermediate Stage/Late Status Epilepticus—10 to 30 Minutes

After 10 minutes, because of the continuous production of GABA as the patient continues to have a seizure, the GABA A-δ_2 subunits start to internalize, leading to loss of almost 20-fold of the benzodiazepine's potency by the end of 30 minutes (Figure 1).[11-13] Thus, benzodiazepines given for a seizure continuing for more than 10 minutes might be less effective to abort a seizure. However, benzodiazepines remain the most effective and most feasible treatment in this period and should always be the first choice in treatment (Table 1).

Late Stage/Refractory Status Epilepticus —More Than 30 Minutes

After 30 minutes, upregulation of the *N*-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors occurs, along with decreased production of the inhibitory neurotransmitters and overproduction of the proseizure neurotransmitters (Figure 1). These changes are mostly responsible for the refractory state. This state is certainly much less responsive to benzodiazepines. Therefore, benzodiazepines given for a seizure continuing for more than 30 minutes might be significantly less effective to abort a seizure. Other alternatives (eg, ketamine and propofol) should be considered after benzodiazepines have been tried and failed (Table 1).

Very Late Stage/Super-refractory Status Epilepticus—24 hours or longer

After 24 to 48 hours of attempts at seizure suppression, a lack of response despite aggressive sedation, or a seizure recurrence within 24 hours of weaning the patient from the sedation, is defined as lack of seizure suppression and called super-refractory status epilepticus. Multiple hypotheses have been proposed for this state, but the etiology remains undetermined. Reversal of GABA properties owing to changes in extracellular ionic environment, cell death secondary to excitotoxicity, and mitochondrial malfunction have all been suggested as etiologic factors.[14] Super-refractory status epilepticus is extremely challenging to treat and has high mortality rates. Expert consultation for other advanced therapies should always be considered in such a scenario (Table 1).

DISCUSSION

These seizure stage timelines are surely not strict cutoffs, and certainly interindividual and intraindividual variability are possible. However, it is helpful clinically to put the stages into an approximate time

Table 1. Comparison of different stages of seizure

Seizure or treatment characteristic	Acute convulsive seizure	Early status epilepticus	Late status epilepticus	Refractory status epilepticus	Super-refractory status epilepticus
Time from seizure onset	< 5 min	5-10 min	10-30 min	≥ 30 min	≥ 24 hours
Role of BZD	Too early	Early	Intermediate	Late	Too late
BBB disruption	-	+	++	+++	++++
Neurotransmitter upregulation	GABA	GABA	GABA	Glutamate, AMPA	Dysregulation
Receptor upregulation	++GABA Aβ, +GABA Aδ	+++GABA Aβ, ++GABA Aδ	+GABA Aβ, +++GABA Aδ	NMDA, AMPA, ++GABA Aδ	Dysregulation
BZD control of seizures	++	+++	+	+/-	-
Other sedatives	Not needed	May or may not give propofol and/or phenobarbital	Propofol and/or phenobarbital	Ketamine, propofol, and/or pentobarbital	Pentobarbital and advanced management
Prominent clinical effect of BZD	With or without cardiorespiratory collapse	Seizure control	Less effective seizure control	With or without seizure control	Usually ineffective

AMPA = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; BBB = blood-brain barrier; BZD = benzodiazepines; GABA = γ-aminobutyric acid; NMDA = *N*-Methyl-D-aspartate; - = none; + = mild; ++ = moderate; +++ = substantial; ++++ = very substantial.

frame that clinicians and practitioners can follow easily, in the hope for better outcomes. Nonetheless, the types of seizure are different, and involvement of the autonomic system is variable from 1 seizure to another. Thus, it is always helpful to take into account the type of seizure if possible. For example, a patient with an autonomic seizure characterized with high sympathetic or parasympathetic outflow might drastically decompensate after a single dose of benzodiazepine. On the other hand, a paient with a seizure with less or no autonomic involvement might be more tolerant to a certain dose of benzodiazepine even if administered early.[6] Thus, although early use of benzodiazepines is highly recommended for termination of status epilepticus, too early use of benzodiazepines for seizure termination (less than 5 minutes) might not be encouraged because of the liability for severe adverse effects in this period. The brain is usually able to self-suppress a seizure in this very early period, and all the patient needs is simple supportive measures and certainly a search for the cause of the seizure. The use of other antiepileptic treatments depends on the clinical scenario.

CONCLUSION

Acute convulsive seizures that do not meet the criteria for status epilepticus should be managed conservatively as most of these seizures are self-limiting. Autonomic involvement with seizures is not very well understood and to the best of our knowledge is variable. Early inhibition of seizures with benzodiazepines can affect the overstimulated autonomic system and therefore can have drastic effects on the cardiorespiratory system. Thus, clinicians and practitioners should be cautious with administering benzodiazepines too early in the seizure course. Further research is needed to clarify the role of benzodiazepines in disrupting the autonomic balance during acute convulsive seizures. ❖

Disclosure Statement

The author(s) have no conflicts of interest to disclose.

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The Falling Sickness

Cassius: But soft, I pray you: What, did Caesar swound?
Casca: He fell down in the market-place, and foamed at mouth, and was speechless.
Brutus: 'Tis very like: He hath the falling sickness.

— Julius Caesar, act I, scene ii; William Shakespeare, 1564-1616, English poet, playwright, and actor